Study Results Synopsis for Public Disclosure

Name of product: FAZ053 and Spartalizumab (PDR001)

Protocol identification number: EudraCT no. 2016-001470-15, ClinicalTrials.gov no. NCT02936102

Title of study: A Phase I, open-label, multi-center dose escalation study of FAZ053 as single agent and in combination with PDR001 in adult patients with advanced malignancies

Study center(s): Study was conducted in 12 centers in 9 countries: Spain (15 participants), Canada (23 participants), Taiwan (1 participant), USA (48 participants,) Singapore (27 participants), Israel (14 participants), Japan (17 participants), Italy (6 participants) and France (3 participants).

Publication (reference): Janku F, Tan DSP, Martin-Liberal J, et al (2025) First-in-human study of FAZ053, an anti-programmed death-ligand 1 (anti-PD-L1) monoclonal antibody, alone and in combination with spartalizumab, in patients with advanced malignancies. ESMO Open. 10(6):105051.

Study period:

Study initiation date: 20-Oct-2016 (first participant first visit)

Early termination date: 09-Jul-2018 (date of recruitment halt)

Study completion date: 22-Nov-2024 (last participant last visit)

Phase of development (phase of this clinical study): I

Objectives:

Primary Objective: To characterize safety and tolerability of FAZ053 as a single agent and in combination with PDR001 and to identify recommended doses and schedules for future studies.

Secondary Objectives:

- To characterize the pharmacokinetic profiles of FAZ053 as single agent and in combination with PDR001
- To assess emergence of anti-FAZ053 and anti-PDR001 antibodies following one or more i.v. infusions of FAZ053 single agent and in combination with PDR001
- To characterize the pharmacodynamics profiles of FAZ053 as single agent and in combination with PDR001
- To characterize changes in the immune infiltrate in tumors following the administration of FAZ053 single agent and in combination with PDR001
- To assess the preliminary anti-tumor activity of FAZ053 as a single agent and in combination with PDR001

Study design and methodology:

This was a phase I, multi-center, open-label study starting with dose escalation of FAZ053 single agent and FAZ053 in combination with PDR001, followed by dose expansion.

FAZ053 as single agent was dose escalated from 80 mg to 240 mg, 800 mg, 1200 mg and 1600 mg every 3 weeks (Q3W). PDR001 300 mg Q3W was combined with escalating doses of FAZ053 from 20 mg to 60 mg, 200 mg, 600 mg, 800 mg and 1200 mg Q3W. FAZ053 single agent was further evaluated in escalating doses, from 800 mg to 1200 mg and 1600 mg every 6 weeks (Q6W). It was planned to have approximately 3 to 6 participants per dosing cohort.

Dose expansion of FAZ053 as single agent or in combination with PDR001 was planned to commence once the maximum tolerated dose (MTD) or recommended dose for expansion (RDE) (if that is lower than MTD) of the Q3W dosing regimen was declared. It was planned to have approximately 35 participants in the expansion arm (triple negative breast cancer (TNBC) = 20 and Chordoma/alveolar soft part sarcoma (ASPS) = 15). Dose expansion of combination therapy was not initiated as the study was terminated due to business reasons.

Diagnosis and main criteria for inclusion:

The study population consisted of both male and female adult participants (≥ 18 years) with advanced solid tumors.

Key inclusion criteria

1. Written informed consent had to be obtained prior to any procedure.
2. Age ≥ 18 years
3. **Dose escalation cohorts of FAZ053 single agent and FAZ053 in combination with PDR001:** participants with advanced/metastatic solid tumors with measurable or non-measurable disease as determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, who may or may not had received prior treatment with an immune checkpoint inhibitor, who had progressed despite standard therapy or for whom no standard therapy was available.
4. **Dose expansion groups of FAZ053 single agent and FAZ053 in combination with PDR001:** participants with advanced/metastatic solid tumors with at least one measurable lesion as determined by RECIST version 1.1, who may or may not had received prior treatment with an immune checkpoint inhibitor (for FAZ053 single agent no treatment with an anti-PD-L1 inhibitor was permitted), who had progressed despite standard therapy or for whom no standard therapy was available and fit into one of the following groups:
    - FAZ053 single agent:
        - TNBC negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2)
        - Chordoma/ASPS
        - Selected indication(s) in dose expansion group Q6W dosing regimen
    - FAZ053 in combination with PDR001:
        - TNBC negative for ER, PR and HER2
        - Chordoma/ASPS
        - Selected indication(s) in dose expansion group Q6W dosing regimen

5. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2
6. Participant was required to have a site of disease amenable to biopsy and be a candidate for tumor biopsy according to the treating institution's guidelines. Participants needed to be willing to undergo a new tumor biopsy at screening, and during therapy on this study. Exceptions might be made on a case-by-case basis after documented discussion with Novartis.

Key exclusion criteria

1. Presence of symptomatic central nervous system (CNS) metastases or CNS metastases that require local CNS-directed therapy (e.g. radiotherapy or surgery) or increasing doses of corticosteroids within the prior 2 weeks. Participants with treated brain metastases were required to be neurologically stable (for 4 weeks post-treatment and prior to study enrollment) and off steroids for at least 2 weeks before administration of any study treatment.
2. History of severe hypersensitivity to study treatment excipients and additives or other mAbs and/or their excipients.
3. Active, known or suspected autoimmune disease. Participants with vitiligo, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger were not excluded. Participants previously exposed to anti-PD-1/PD-L1 treatment who were adequately treated for skin rash or with replacement therapy for endocrinopathies were not excluded.
4. Treatment with cytotoxic or targeted antineoplastics within 3 weeks of initiation of study treatment. For cytotoxic agents that had major delayed toxicity a washout period of one cycle was indicated (examples are nitrosoureas and mitomycin C which typically require a 6-week washout period). Prior antibodies or immunotherapies that required 6 weeks of washout.
5. Participants who received systemic chronic steroid therapy or any immunosuppressive therapy (≥ 10 mg/day prednisone or equivalent). Although topical, inhaled, nasal and ophthalmic steroids were allowed.
6. Active infection that required systemic antibiotic therapy.

Test and reference therapies, dose and mode of administration, batch number:

FAZ053 and PDR001 were administered via intravenous (i.v.) infusion. No reference therapy was administered.

Protocol amendments and other changes to study conduct:

This summary describes the conduct of the study according to the final protocol (including all 7 amendments). The final protocol was dated 11-May-2023. The key features of each amendment are presented in Table 2-1.

Since the study was conducted during the COVID-19 pandemic, local COVID-19 pandemic situations were monitored in close collaboration between the clinical trial teams, the study sites, the local organizations of the Sponsor and regulators according to relevant internal and local guidelines. All on-site visits and assessments of the enrolled participants were completed as planned in the protocol.

As a result of the decision to halt participant enrollment, effective 09-Jul-2018, FAZ053 Q3W in combination with PDR001 expansion arm was not opened. Summaries of concomitant medication were removed from the analyses.

On 18-Sep-2023, during the conduct of this study, the database was transitioned from OC RDC to Rave, with no impact on the data flow or data quality.

Table 2-1 Protocol amendments

Version and date	Summary of key changes
Amendment 7 (11-May-2023)	• The interval for computerized tomography (CT) scans was to be performed at least once every 6 cycles (every 18 weeks ± a 21-day window). • The requirement for disease progression follows up for participants who discontinue from study treatment for reasons other than disease progression was removed. • Blood sampling for coagulation, glucose evaluation, and thyroid function was reduced.
Amendment 6 (08-Oct-2020)	• The definition of EoS was revised. • The participants who were still on treatment and had completed over 30 treatment cycles during which an adequate number of blood and biomarker samples were collected. The specific samples were no longer collected: - Blood samples for pharmacokinetic (PK), receptor occupancy (RO), sPD-L1 and immunogenicity (IG) at the end of treatment (EoT) visit and at the 150 day safety follow-up visit. - Tumor samples at every eight cycle visits and at progressive disease. - Blood samples for cfDNA at every two cycle visits.
Amendment 5 (17-Aug-2018)	• The expansion part for FAZ053 in combination with PDR001 was not to be opened. • Study treatment may also be discontinued if progressive disease was determined per RECIST 1.1 or as determined by the investigator. • Disease progression follow up was no longer applicable in case the study was terminated. • If an inadequate tumor sample was received at screening following a new biopsy procedure (e.g. found to have low tumor content), an archival tumor may be requested to allow for the analysis. • Up to five new measurable lesions (maximum of two per organ) were allowed to be included in the overall tumor assessment.
Amendment 4 (17-Apr-2018)	• It was highlighted that the expansion arms would focus on the evaluation of participants with TNBC, chordoma and ASPS.

Version and date	Summary of key changes
	• It was allowed for participants with FAZ053 single agent, in the dose escalation or dose expansion part, who have demonstrated CR/PR per RECIST v1.1 may, upon radiological disease progression per RECIST v1.1, switch to FAZ053 in combination with PDR001 at a combination dose level that has been tested in the dose escalation and meets the EWOC principle. Participants were not eligible to switch to combination treatment if they experienced any AE > Grade 2 related to treatment while receiving FAZ053 single agent. • The use of condom for male study participants receiving PDR001 and/or FAZ053 was no longer required. • Disease progression follow up visit was added to ensure tumor evaluation assessments were collected, as applicable. • Personal data definition and withdrawal of consent revisions were made in order to incorporate and reflect the European Economic Area (EEA) General Data Protection Regulations (GDPR) requirements. • Pregnancy follow-up was revised from 3 months to 12 months.
Amendment 3 (18-May-2017)	• The secondary endpoint related to the characterization of PD profiles of FAZ053 was updated. • It was clarified that concomitant medications would be collected until the 30 day safety follow-up has been completed, or the start of a new antineoplastic therapy, whichever occurs first. • Only suspected AEs and suspected SAEs were collected after 150 day (during safety follow up period). • Information regarding the full neurological exam was updated. • To align with the EMA standard term list, the PDR001 pharmaceutical form was updated to “powder for solution for infusion”.
Amendment 2 (11-Oct-2016)	• Exclusion Criteria: Clarification that participants with a history of current drug-induced interstitial lung disease (ILD) were excluded. • Section 6.3.1: In table 6-5 it was clarified that participants should be discontinued from treatment if a grade 2 infusion reaction recurs at a reinitiated slow rate of infusion and despite oral pre-medication. • For Japan only - Section 7.2.2.1: It was clarified that oxygen saturation (SpO2) would be measured by pulse oximetry for Japanese participants every time physical examination was performed. - Section 7.2.2.8 section was added to clarify that chest x-rays would be performed for Japanese participants at screening and cycle 1 day 11.
Amendment 1 (24-Aug-2016)	• Q6W dosing regimen was added in the protocol. • Inclusion criteria 3 and 4: it was clarified that only participants who had progressed despite standard therapies or for whom no standard therapy is available, could enroll. • Exclusion Criteria: participants with a history of severe hypersensitivity to excipients of other monoclonal antibodies were excluded; participants with a history of pneumonitis or current pneumonitis were excluded, even if it was not drug-induced; participants with radiotherapy within 2 weeks prior to the first dose of study drug were excluded, except for palliative radiotherapy to a limited field. • Clarification was provided: in case the dose (as single agent or in combination) was delayed recovering from previous AEs, dosing might resume once the AEs had resolved to grade 1 or baseline and the start of the next cycle would shift accordingly. • Clarification that for participants with anaplastic thyroid cancer, focal irradiation was allowed to a target lesion if it was life-threatening provided that other measurable disease remained. • Section 6.1.1 and Section 7.2.2.2: It was clarified that there should be a period of at least two hours after the infusion whereby the participant requires close observation.

Version and date	Summary of key changes
	• Criteria for defining dose-limiting toxicities: It was clarified that total bilirubin ≥ 2x ULN with ≥ CTCAE Grade 3 AST/ ALT was a DLT. It was clarified that all grade 3 or 4 electrolyte abnormalities were DLTs. The following new DLT was added: Grade 2 AE resulting in a dose delay of >7 days and does not resolve to grade 1 within 14 days. It was clarified that any grade reduction of visual acuity was a DLT. • Section 6.3.1: It was clarified that for DLTs occurring during the DLT observation period, participants must discontinue study treatment with the exceptions outlined in Table 6-5 and Appendix 4 • Recommended dose modification: Guidelines that were clinically significant and thought to be immune-related were modified. • Safety follow-up evaluations at 30 and 90 days after the last dose of study treatment was added • During the 150 days safety follow-up period, after initiation of new antineoplastic therapy only AEs and SAEs suspected to be related to the study treatment were collected. • Frequency of thyroid function tests was increased to every 2 cycles (every 6 weeks).

Criteria for evaluation:

Safety and tolerability: Safety was monitored by assessing physical examination, vital signs, body height and weight, ECOG performance status, neurological assessment, laboratory evaluation (hematology, chemistry, coagulation, glucose monitoring, thyroid function, cytokines), pregnancy, ECG, as well as collecting of the adverse events (AEs) at every visit.

Efficacy: Tumor response was determined locally according to two sets of criteria; RECIST v1.1 and irRC. Local assessments conducted by the investigators were used to analyze responses according to both RECIST v1.1 and irRC, for treatment decision making.

Pharmacokinetics immunogenicity, PD-L1, and receptor occupancy: The following PK parameters were determined for FAZ053 single agent, and FAZ053 in combination with PDR001 using non-compartmental methods: Cmax, Tmax, AUC0-tlast and AUCtau (C1D1 and C3D1 for Q3W, and C5D1 for Q6W), time to last measurable concentration (Tlast), Clast, T1/2 (where feasible), and the accumulation ratio of FAZ053 and PDR001. Immunogenicity samples were also collected to monitor the appearance of anti-drug antibodies. PK and immunogenicity (IG) samples were collected in the event of a clinically significant AE (such as infusion reaction/anaphylaxis) or, if IG against the study treatment was suspected in any samples, they were used to measure relevant biomarkers to better understand the infusion reaction/AE. Soluble/shed PD-L1 and Receptor Occupancy (RO) for FAZ053 were also assessed at regular intervals throughout the treatment period.

Biomarkers: paired tumor samples were collected to assess the pharmacodynamics effect of FAZ053 administered as a single agent and in combination with PDR001 on the tumor microenvironment. In this study, given that CD8+ T cells were the most relevant subset of lymphocytes to track, only CD8+ biomarkers were analyzed and not tumor-infiltrating lymphocytes (TILs).

Statistical methods:

- The data was analyzed by Novartis personnel using SAS version 9.4, and for Bayesian modeling, R version 3.0.2 and JAGS version 3.4.0. PK parameters were calculated using non-compartmental methods available in Phoenix WinNonlin version 8.3.
- Data from participating centers in the study protocol were combined to have an adequate number of participants for analysis. No center effect was assessed.

- Data was summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data).
- Participants treated with the same dose level and schedule of FAZ053 were pooled into a single dosing cohort (includes participants from dose escalation and dose expansion parts).
- **Primary endpoints:**
  - The assessment of safety was based on the type and frequency of AEs as well as on the number of laboratory values that fall outside of pre-determined ranges (CTCAE V4.03 grading limits or normal ranges as appropriate).
  - The dose escalation part was based on the Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle.
- **Secondary Endpoints:**
  - For all efficacy parameters, data were listed, summarized, or analyzed by dosing cohort.
  - Overall Response Rate (ORR) was summarized as point estimate and corresponding to 95% exact confidence interval (CI). The Bayesian approach was used for estimation of the distribution of ORR and to provide inferential summaries in dose expansion groups.
  - Disease Control Rate (DCR) was summarized by dosing cohort with 95% CI. If there were a large number of participants in dose expansion achieving response (e.g., ≥ 5%), the Kaplan-Meier plots for Duration of Response (DOR) were produced and the median DOR by indication was estimated
  - A Kaplan-Meier plot for Progression Free Survival (PFS) was presented for each indication in the dose expansion part if enough number of participants (≥ 10) were enrolled for an indication. Median PFS (in months) with corresponding 95% CI, 25^{th} and 75^{th} percentiles and Kaplan- Meier estimated probabilities (PFS rate) with corresponding 95% CIs at several time points were presented.
  - PK concentration data was summarized by treatment and timepoint. In addition to descriptive statistics, graphical presentation of arithmetic mean (± SD) plasma concentrations for FAZ053 and PDR001 at each scheduled timepoint were provided. PK parameters were calculated using non-compartmental methods and summarized as using descriptive statistics.
  - The analysis of dose proportionality was conducted for AUCtau and Cmax of single agent FAZ053 using a linear model on log-transformed scale.
  - Pharmacodynamic (PD) markers, PD-L1 receptor occupancy and soluble/shed PD-L1 concentrations were listed by participant and time point and summarized using descriptive statistics by dosing cohort. In addition to descriptive statistics, graphical presentation of individual profiles and/or arithmetic mean (±SD) of soluble/shed PDL-1 levels were provided.
  - CD8 expression was measured by immunohistochemistry (IHC) and reported as percentage marker area and tumor area (mm^2). For each IHC measurement the mean, standard deviation, % CV, median, minimum, maximum, inter-quartile range at baseline and post-baseline (C3D1) were reported. Absolute and relative change (percent change) from baseline was calculated for each participant and reported by dosing cohort.
  - A summary (n and %) and listing of ADA participant status and ADA sample status was provided.

Summary - Results

Demographic and background characteristics:

- The median age of the participants was 58 years (range: 25–79 years), 59 years (range: 32– 77 years) and 58 years (range: 27–77 years) for participants treated with FAZ053 single agent Q3W, FAZ053 single agent Q6W and FAZ053 single agent Q3W in combination with PDR001, respectively.
- The majority of the participants were female for FAZ053 single agent Q3W treatment arm (60.5%) and FAZ053 single agent Q3W in combination with PDR001 treatment arm (65.6%). FAZ053 single agent Q6W treatment arm had nearly balanced distribution of male (9/17, 52.9%) and female (8/17, 47.1%) participants.
- Majority of the participants were Caucasian for all the treatment arms.
- At baseline, the median body mass index (BMI) of the participants was 25.3 kg/m^2 (range: 14.0–41.8 kg/m^2), 26.2 kg/m^2 (range: 17.9–33.6 kg/m^2) and 24.6 kg/m^2 (range: 16.6–44.3 kg/m^2) for participants treated with FAZ053 single agent Q3W, FAZ053 single agent Q6W and FAZ053 single agent Q3W in combination with PDR001, respectively.
- All the participants had an ECOG performance status < 2.

Protocol deviations:

- Fifteen participants (15/76, 19.7%) who received FAZ053 single agent Q3W incurred protocol deviations. The most frequently reported deviation was 'key safety procedure not performed as per protocol' (5/76, 6.6%).
- Four participants (4/17, 23.5%) who received FAZ053 Q6W incurred protocol deviations. The most frequently reported deviation was 'procedure at baseline not performed as per protocol' (2/17, 11.8%).
- Thirteen participants (13/61, 21.3%) who received FAZ053 Q3W in combination with PDR001 incurred protocol deviations. The most frequently reported deviation was 'procedure at baseline not performed as per protocol' (3/61, 4.9%).

None of the reported protocol deviations were considered to have had a significant impact on the participants' safety or the interpretations of the study results.

Exposure:

- For FAZ053 single agent Q3W dose escalation and expansion treatment arm: A total of 76 participants were treated with FAZ053 single agent Q3W. The median duration of exposure (DOE) of FAZ053 was 15.1 weeks (range: 2.9–321.4 weeks) and relative dose intensity (RDI) was 100% (range: 96.6–100.0).
- For FAZ053 single agent Q6W dose escalation treatment arm: A total of 17 participants were treated with FAZ053 single agent Q6W. The median DOE of FAZ053 was 12.4 weeks (range: 3.4–78.0 weeks) and RDI was 100% (range: 100.0–100.0).
- For FAZ053 Q3W in combination with PDR001 dose escalation treatment arm: A total of 61 participants were treated with FAZ053 Q3W in combination with PDR001. The median DOE of FAZ053 in combination PDR001 was 12.1 weeks (range: 1.6–203.0 weeks) and RDI for both FAZ053 and PDR001 was 100% (range: 97.5–100.0 and 100.0-100.8, respectively).

Efficacy results:

- In dose escalation, the ORR by investigator assessment was 4.8% (Partial Response (PR): n = 2) for FAZ053 single agent Q3W, 5.9% (PR: n =1) for FAZ053 single agent Q6W, and 4.9% (PR: n = 3) for FAZ053 Q3W in combination with PDR001 300 mg Q3W.
- In dose expansion with FAZ053 single agent 1200 mg Q3W, the ORR by investigator assessment for TNBC, chordoma and ASPS was 10.0% (PR: n = 2), 30% (Complete Response (CR): n = 1, PR: n = 2) and 50% (PR: n = 2), respectively.
- The estimated ORR for TNBC was 0.10 (95% CI: 0.015, 0.260), with the estimated probability of 0.01 for the true ORR falling within the interval of substantial efficacy. For chordoma/ASPS, the estimated ORR was 0.34 (95% CI: 0.134, 0.588) and the estimated probability for the true ORR falling within the interval of substantial activity [30% to 100%] was 0.611.
- In dose escalation, the median PFS per RECIST v1.1 was 2.1 months (95% CI: 2.0, 3.6) for the FAZ053 single agent treatment arm and 2.4 months (95% CI: 2.1, 4.2) for the combination treatment arm.
- In dose expansion with FAZ053 single agent 1200 mg Q3W, the median PFS per RECIST v1.1 for TNBC, chordoma, and ASPS was 1.7 months (95% CI: 1.1, 4.0), 18.8 months (95% CI: 1.8, NE) and 34.5 months (95% CI: 3.6, NE), respectively.
- Kaplan-Meier analyses of DORs were not performed due to the small number of responders.
- Findings per irRC were consistent with those per RECIST v1.1.

Pharmacokinetic results:

- For FAZ053 single agent Q3W estimated terminal half-life for both cycles increased with dose up to 800 mg, stabilizing thereafter. For FAZ053 in combination with PDR001 300 mg Q3W, the estimated terminal half-life for C1D1 increased with dose up to 600 mg and generally stabilized thereafter, while for C3D1 it showed no dose dependency. For FAZ053 single agent Q6W estimated mean terminal half-life for C1D1 ranged from 16.3 to 20.3 days.
- Modest FAZ053 accumulation was observed following Q3W regimen. Racc (based on AUCtau) for FAZ053 single agent Q3W, FAZ053 single agent Q6W and FAZ053 in combination with PDR001 300 mg Q3W was 1.04–1.76, 0.96–1.64 and 1.01 to 1.57, respectively.
- FAZ053 exposure (AUCtau and Cmax) increased approximately in proportion to dose for FAZ053 single agent Q3W. For FAZ053 single agent Q6W dose proportionality of overall exposure (AUC) was not confirmed due to limited available data.
- Since the PK profiles of PDR001 were similar when combined with FAZ053 at different dose levels, it is concluded that FAZ053 has no effect on the PK of PDR001.
- The PK variability of both PDR001 and FAZ053 were low to moderate.

Pharmacodynamic results:

- For the FAZ053 single agent Q3W treatment arm, < 10 participants contributed samples to derive RO data in most dosing cohorts and the range of RO (min–max) appeared wide across the sampling time points. For FAZ053 single agent Q6W treatment arm, RO data was

available for only 1 participant, thus limiting the ability to draw meaningful conclusions on receptor engagement.

- Total sPD-L1 level remained ≤ 2 ng/ml, ≤ 2.11 ng/ml and ≤ 2.17 ng/ml in participants treated with FAZ053 Q3W, FAZ053 Q6W and FAZ053 Q3W in combination with PDR001, respectively.
- The mean absolute percentage change from baseline of CD8+ T-cells area in tumor biopsy samples obtained for the FAZ053 Q3W, FAZ053 Q6W and FAZ053 Q3W in combination with PDR001 300 mg Q3W treatment arms was 1.56% (range: 0.00–11.54), 4.73% (range: 0.05–20.11) and 1.57% (range: 0.02–6.43), respectively. CD8+ T-cells biomarker values were not available for participants treated with 800 mg and 1200 mg FAZ053 Q3W in combination with PDR001 300 mg Q3W.

Immunogenicity

- In participants treated with FAZ053 single agent who contributed baseline and post-baseline samples for evaluation, the incidence of treatment-induced ADA-positivity for FAZ053 was 20.3% (15/74), most of which was reported in the Q3W treatment arm.
- In participants treated with combination therapy who contributed baseline and post-baseline samples for evaluation, the incidence of treatment-induced ADA-positivity for FAZ053 was 46.2% (24/52) most of which was reported in participants treated with FAZ053 at doses ≤ 200 mg Q3W. The incidence of treatment-induced ADA-positivity for PDR001 was 11.5% (6/52).

Safety results:

FAZ053 single agent Q3W dose escalation and expansion (n = 76)

- The median DOE to FAZ053 was 15.1 weeks and RDI was 100.0%.
- No dose-limiting toxicities (DLTs) were reported.
- FAZ053 single agent 1200 mg Q3W and 1600 mg Q4W were declared RDEs based on an overall assessment of posterior summaries of DLT rates, safety, efficacy, PK and PD findings.
- Treatment-related adverse events (TRAEs) were reported in 43 participants (56.6%). The most frequently reported TRAEs were fatigue (15.8%), pruritus (10.5%) and hypothyroidism (9.2%). Five participants (6.6%) experienced grade ≥ 3 TRAE.
- Four participants (5.3%) died during the treatment and 30 days follow-up period, due to study indication and other (2.6% each).
- Treatment-related serious adverse events (TRSAEs) were reported in 4 participants (5.3%). Grade ≥ 3 TRSAEs (3.9%) observed were arthralgia, blood creatine, phosphokinase increased, and hepatic function abnormal, reported in 1 participant each.
- AEs regardless of causality leading to discontinuation of study treatment were reported in 7.9% participants and dose adjustments/interruptions among 31.6% participants.
- The majority (85.5%) of participants required additional therapy for AEs, regardless of causality.
- The most frequently reported grade 3/4 hematological abnormalities were decreased hemoglobin (Grade 3: 6.6%) and absolute lymphocyte (Grade 4: 1.3% and Grade 3: 6.6%).

- Grade 4 lipase increase and calcium corrected decrease was observed in 1 participant (1.3%), each. The most frequently reported grade 3 clinical abnormalities were increased lipase (9.2%), AST (6.6%), alkaline phosphatase (5.3%) and amylase (5.3%), as well as reduction in phosphate (2.6%).
- Overall, no clinically significant vital signs and electrocardiogram (ECG) abnormalities were reported.

FAZ053 single agent Q6W dose escalation (n = 17)

- The median DOE to FAZ053 was 12.4 weeks and RDI was 100.0%.
- One participant (5.9%) in 1600 mg dosing cohort experienced DLT of grade ≥ 3 renal failure.
- TRAEs were reported in 8 participants (47.1%). The most frequently reported TRAEs were fatigue; pruritus; rash and diarrhea (11.8% each). One participant (5.9%) experienced grade ≥ 3 TRAE.
- One participant (5.9%) treated with FAZ053 1600 mg Q6W died of renal failure during the treatment and 30 days follow-up period, which was suspected to be related to FAZ053. The fatal outcome was due to discontinuation of supportive measures (hemodialysis) as per participant's request.
- TRSAEs of grade ≥ 3 renal failure was reported in 1 participant (5.9%).
- Dose adjustments/interruptions due to AEs were reported in 1 participant (5.9%).
- The majority of the participants (76.5%) required additional therapy for AEs regardless of causality.
- The most frequently reported grade 3 hematological abnormalities were decreased absolute lymphocyte (11.8%) and hemoglobin (5.9%).
- Grade 4 calcium decrease was observed in 1 participant (5.9%). The most frequently reported grade 3 clinical abnormalities were increased amylase, total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as well as reduction in potassium (5.9% each).
- Overall, no clinically significant vital signs and ECG abnormalities were reported.

FAZ053 Q3W in combination with PDR001 300 mg Q3W dose escalation (n = 61)

- The median DOE of FAZ053 in combination PDR001 was 12.1 weeks and RDI for both FAZ053 and PDR001 was 100.0%.
- One participant (1/50, 2%) in FAZ053 20 mg dosing cohort experienced DLT of grade ≥ 3 liver function test increased.
- No RDE was declared for FAZ053 Q3W in combination with PDR001 300 mg Q3W dose escalation arm.
- TRAEs were reported in 35 participants (57.4%). The most frequently reported TRAEs were fatigue (23.0%), diarrhea (13.1%;) and nausea (11.5%). Three participants (4.9%) experienced grade ≥ 3 TRAE.
- Six participants (9.8%) died during the treatment and 30 days follow-up period primarily due to study indication.
- One participant (1.6%) experienced TRSAE of grade ≥ 3 autoimmune hepatitis.
- Dose adjustments/interruptions due to AE were reported in 14 participants (23.0%).

- Forty-nine participants (80.3%) required additional therapy for AEs regardless of causality.
- Adverse events of special interest (AESIs) were reported in 38 participants (62.3%; grade ≥ 3: 14.8%). The most frequently occurring AESIs were immune mediated colitis (26.2%; grade ≥ 3: 4.9%), skin reaction (24.6%; grade ≥ 3: 0) and liver enzyme increase (investigations) (19.7%; grade ≥ 3: 4.9%).
- The most frequently reported grade 3 hematological abnormalities were the reduction in lymphocytes (14.8%) and hemoglobin (6.6%).
- The most frequently reported grade 3 clinical abnormalities were increased alkaline phosphatase (9.8%), lipase (4.9%) and AST (4.9%), as well as reduction in sodium (9.8%).
- Overall, no clinically significant vital signs and ECG abnormalities were detected.

Conclusions:

Overall, this study showed that FAZ053 with and without PDR001 administered to participants with advanced malignancies was safe and tolerable. Clinical laboratory parameters and vital signs remained stable throughout the study for the majority of participants. No clinically significant ECG abnormalities were observed.

The inclusion of very rare sarcomas without prespecified sample sizes resulted in the treatment of relatively fewer participants with ASPS and chordoma, which was compounded by the lack of control groups, and ultimately limited the statistical robustness of the findings of dose expansion arm of this study. Based on the early efficacy signal observed in participants with advanced chordoma treated with FAZ053, further evaluation with robust predefined correlative science is warranted.